Calcium Stone Disease

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Outline

- Pathogenesis
- Primary Hyperparathyroidism
- Idiopathic Hypercalcemia
- Hypercalciuria
- Hyperuricosuria
- RTA
- Hypocitraturia
- Idiopathic Calcium Lithiasis
- Hyperoxaluria

Calcium stone Disease

- Majority of patient’s stone disease tends to accelerate
- In a minority of cases the severity of disease lessens
- Cannot distinguish based on metabolic disorder, age, or sex

Pathogenesis: Saturation

- Undersaturation: Solution with calcium oxalate crystals that neither grow or shrink
- Ca++ and oxalate concentrations unchanged--system in equilibrium
- Lower free ion activity and the crystals will dissolve
- A higher free ion activity will cause the crystals to grow

Saturation

- **Metastability--when the crystals grow**
- **Unstable--when there is a creation of new crystal nuclei**
- **Renal excretion of Ca++, oxalate, PO4, and water is a primary determinant of saturation**
- **Binding Ca and oxalate or changing solution pH alter free ion concentrations**
- **Ion binding complicates measurement of urine saturation**
- **Hypercalciuria, oxaluria, hypocitraturia, alkaline urine and long term dehydration increase risk of stones (but do not ensure stone formation)**

Urine Saturation Measurement

- Robertson and associates calculated urine free ion activity for Ca, oxalate, and po4
- Activity Product Ratio (APR) calculated by dividing ion activity product by equilibrium solubility product
- Ratio > 1 oversaturation, below 1 undersaturation
- APR at which solid forms is the Formation Product Ratio

Urine Saturation Measurements

- Robertson, Pak, and Weber et al found that stone former's urine is more supersaturated than normal
- Observed that normal urine is usually above the equilibrium solubility product and is oversaturated
- Added crystals grow in urine from most normal persons

Nucleation

- Spontaneous formation of new crystal nuclei in an oversaturated solution
- Particles of dust, debris, other crystals furnish surface for other crystals to form
- Epitaxis refers to the efficiency of heterogeneous nucleation between a preformed surface and a new crystal
- Monosodium urate and uric acid are excellent heterogeneous nuclei for calcium oxalate

Crystal Growth and Aggregation

- Crystal nuclei grow if they are suspended in urine with an APR above 1
- Growth rate increases with the extent of oversaturation and tends to most rapid with highest values of APR
- Urine from stone formers contains larger crystal aggregates than does urine from non-stone formers

Growth, nucleation, and aggregation

- Urine crystal growth rate is lower than salt solution with same APR
- Urinary pyrophosphate inhibits calcium phosphate crystal formation
- Nephrocalcin (urinary glycoprotein) has been found to inhibit calcium oxalate crystal growth and nucleation
- Nephrocalcin from urine in stone formers has been found to be abnormal
- Tamm-Horsfall protein inhibits calcium oxalate crystal aggregation.
- In a study from a group of pts with accelerated nephrolithiasis, TH protein didn’t inhibit aggregation normally

Main Established Stone forming conditions

- Oversaturation
- heterogeneous nucleation
- reduced inhibitors

Occurrence rates and pathogenetic mechanism

	Oversaturation	nucleation	Reduced inhibition of stone formation
Primary hyperparathyroidism	+	+	-
Idiopathic hypercalciuria	+	-	?
Hyperuricosuria	-	+	+
RTA	+	?	?
Hyperoxaluria	+	-	?
Idiopathic lithiasis	-	-	+

Primary Hyperparathyroidism

- Chronic over secretion of PTH with resultant hypercalcemia
- In past--osteitis fibrosa cystica or renal calculi have been basis for its detection
- now--biochemical screening, majority asymptotic
- 85-95% from single parathyroid adenoma
- 5-15%-from four gland hyperplasia (Men Syndrome)
- Carcinoma <1%
- Around 7 percent of patient’s with Calcium Stone Disease

Hormones and Calcium

	Action			Result	
Hormone	**bone**	**kidney**	**intestine**	**Serum calcium**	**Serum phos**
PTH	Ca resorption	Phos excretion Activate v. D Ca reabsorption	Increased Ca absorption (Via Vit D)	Increased	Decreased
1,25 Vit D	Ca resorption	Increased Ca reabsorption	Increased Ca and PO4 absorption	Increased	Increased

Parathyroid Hormone

- Negative Feedback by Ca and Mg
- Rapidly metabolized in liver and Kidney
- Smaller fragment (aminoterminal) biologically active
- Calcium intestinal absorption increased in hyperparathyroidism via stimulation of 1,25 (produced in kidney)

Parathyroid Hormone

- PTH-->bone resorption, increased Ca release
- Increases distal tubular Ca reabsorption
- Hyperparathyroidism causes further tubular Ca reabsorption (even with calcium restricted diet)
- Urinary calcium excretion may then become greatly increased

Stone Formation

- Usually calcium oxalate, brushite or uric acid, or combinations
- often recur and become bilateral
- nephrocalcinosis may be only manifestation of hyperparathyroidism
- APR for calcium oxalate is elevated in patients with hyperparathyroidism secondary to increased Ca concentration
- FPR decreased, which is an unexplained phenomenon

Diagnosis

- Demonstration of hypercalcemia and exclusion of other causes
- Multiple Calcium levels should be taken
- immunometric assays recognizing only the intact PTH level by using two antibodies directed against two different sites of the iPTH molecule

Familial Hypocalciuric Hypercalcemia

- Hypercalcemia with normal or low urinary calcium
- iPTH levels may be elevated, but hypocalciuria is not dependent on PTH
- Do not form calcium stones
- Urinary Ca/Creatinine clearance ratio of .01 or below helps distinguish from hyperparathyroidism

Treatment for Hyperparathyroidism

- Removal of adenomatous/hyperplastic gland(s) in patient with stones or bone disease, pancreatitis, PUD, muscle weakness, ms changes, or Ca > 12
- Perform biopsy on all four glands at surgery
- Post op hypo Ca, Mg, PO4, “Hungry Bone Syndrome”
- Hypo Ca with Hyperphos could mean temporary or permanent hypoparathyroidism

Treatment for Hyperparathyroidism
Medical Management

- Estrogen or progestin reduce serum Ca and may slow bone loss in post menopausal woman
- Estrogen inhibits PTH action on bone
- Dietary Salt restriction reduces urinary Ca excretion
- Bisphosphonates inhibit osteoclast function, long term effects of this treatment are unknown

Idiopathic Hypercalciuria

33 percent

- 30-40% Ca Stone formers excrete more Ca than normal
- 300mg/day men, 250 mg/day for woman, or 4mg/kg/day
- R/O other causes of hypercalciuria
- 2-4% of adults, 80-90% idiopathic hypercalciuria is silent
- Autosomal Dominant and x linked recessive traits have been described
- Excessive Ca intestinal absorption or depressed renal tubular reabsorption

Intestinal Calcium Absorption

- Normal pt absorb 27-52% of an oral dose of calcium
- Idiopathic Hypercalciuric pt absorb 22-80% (vast overlap)
- Study where 200 to 300 mg of Ca absorbed, 0/38 normal patients excreted 300 mg Calcium in urine where as 15 of 16 hypercalciuric pts did

Renal Tubule Calcium Reabsorption

- Generalized defect in proximal tubule reabsorption of fluid and electrolytes
- Increased activity of Ca,Mg ATPase in RBC of IHC patients
- Fractional Ca excretion higher in IHC patients

The Debate

- 2 groups: intestinal overabsorption or renal tubule Ca leak
- Overabsorption-->Postprandial elevation in Ca-->increased filtered load
- Renal leak-->secondary hyperparathyrioidism-->further renal losses--> 1,25 vit d increases
  -->intestinal hyperabsorption

Distinguishing hyperabsorption from renal leak

- Pak and associates found a majority of patients exhibited increased absorption, but there still was an unexplained high frequency of negative Ca balance
- Vit D excess activity? Intestinal overabsorption, increased bone resorption, reduced renal Ca reabsorption
- Still area of controversy

Therapy

- Difficult since pathogenesis is unclear
- Low Ca diet often advocated, but run risk of decreasing bone mineral density
- low Na diet decreases Ca excretion, increased protein diet increases Calcium excretion--not tested in randomized fashion
- Thiazide diuretics decrease Ca excretion

Dietary Considerations.

- Reduce Ca intake if excessive, if hyperoxaluria is present calcium restriction should not be undertaken
- If hyperoxaluria is present, restrict spinach, cranberries, tea, cocoa, and nuts
- In hyper calciuria, restrict NaCl to 6g/day
- Hyperuricosuria--restrict meat intake to 8-10 oz per day
- 2 liters urine output per day

A Prospective Study of Dietary Calcium and other Nutrients and the Risk of Symptomatic Kidney Stones

Stampfer et al, NEJM 1993

- Prospective of Relations between dietary Ca intake and risk of symptomatic kidney stones in a cohort of 45,619 men
- Dietary Ca measured by means of a food frequency questionnaire
- 4 year follow up, 505 cases of kidney stones were documented
- Dietary Calcium intake inversely associated with risk of kidney stones
- 797+/-280 vs 851+/-307mg per day calcium
- Adjustment for age, profession, thiazide use, and intake of animal protein, potassium, alcohol, and fluid attenuated the protective effect of dietary calcium (remained sig)

Comparison of Dietary Calcium with Supplemental Calcium and other Nutrients as Factors Affecting the Risk for Kidney Stones in Woman

Stampfer, Annals of Internal Medicine, 1997

- Objective: Examine association between intake of calcium and risk for kidney stones in woman
- 91731 woman in Nurse's health study
- 903,849 person years, 864 cases of kidney stones
- Intake of dietary calcium was inversely associated with risk for kidney disease
- Dietary calcium reduces absorption of oxalate

Summary of 1997 study

- Support hypothesis that high intake of dairy products decrease risk of stones
- High intake of nonfood Ca supplements increase this risk
- Routine restriction of dairy products should not be recommended
- Risk for stone formation may possibly be reduced if supplement is consumed with meals.

Urinary oxalate may play an even more important role than urinary calcium in the process of stone formation because saturation of urine with calcium oxalate increases more rapidly with increases in oxalate concentration than increases in calcium concentration.

Calcium Oxalate Nephrolithiasis: Defective Oxalate Transport.

Kidney Int. 1991

Hyperuricosuria (26 percent)

- Nl uric acid excretion 800mg men and 750 mg for woman
- Stone disease usually seen at later age
- mechanism unclear
- Allopurinol effective treatment

Causes of hyperuricosuria

- High purine diet (but not always)
- Studies have shown that people oversecrete uric acid despite purine free diet
- Assumed to be over production of uric acid during course of endogenous purine metabolism
- In one study of 121 hyperuricosuric patients, 22 % were hyperuricemic

Mechanism of Stone Formation

- Seed crystals of Sodium Hydrate urate initiate calcium oxalate crystals
- Hyperuricosuria increases urine supersaturation with respect to sodium hydrogen urate
- Another implication is undissociated uric acid in acid urine may serve as source of heterogeneous nucleation--but proof is lacking
- Adsorption of crystal growth inhibitors by urate and uric acid crystals increases mass of uric acid crystals and in this manner predispose to calcium stones.

Treatment

- Ettinger and Colleagues performed a RDB trial of allopurinol in hyperuricosuric, normocalciuric patients who formed calcium oxalate stones.
- .26 stones per patient per year (placebo)
- .12 stones/patient/year in allopurinol group
- Pak and Peterson showed that Potassium Citrate also decreased the number of stone recurrences.
- The citrate lowers the calcium oxalate supersaturation and may inhibit urate-induced crystallization of calcium oxalate.

Renal Tubular Acidosis

- Distal RTA is a cause of nephrocalcinosis and renal stone formation in hereditary or sporadic variety
- Acquired RTA does not cause stones
- Proximal RTA and other forms of RTA are not known to cause stones

Hypercalciuria (RTA)

- Intestinal Ca Absorption not elevated
- Metabolic acidosis causes Hypercalciuria
- Hypercalciuria is not always secondary to acidosis (it may predate RTA)
- Some families with hereditary distal RTA have shown dominant inheritance of hypercalciuria

Stone Formation (RTA)

- Elevated urinary calcium and phosphate
- Alkaline urine pH increases availability of PO4 and HPO4 which are incorporated into octocalcium PO4 and brushite
- Citrate excretion is reduced
- Reduction of Ca binding of citrate raises supersaturation with calcium oxalate and calcium phosphate
- Alkali administration tends to reduce stone formation and slow progression of nephrocalcinosis
- one study showed 2 new stones/43 pt years of alkali tx vs 96 stones/100 pt years (pre treatment arm)

Hypocitraturia

- Found in 15-65% of stone formers
- Isolated abnormality or associated with other stone forming risk
- Invariably found in distal RTA
- Chronic diarrhea, diuretic induced hypokalemia, idiopathic

Renal Excretion of Citrate

- Freely filtered by glomerulus
- 65-90% reabsorbed in prox tubule
- Used in oxidative metabolism
- No tubular secretion
- Alkalosis increases/Acidosis decreases renal citrate excretion
- Hypokalemia reduces urinary citrate as well

Stone formation

- Citrate binds Ca-->lower supersaturation of calcium salts
- Citrate has mild calcium oxalate crystal growth inhibition
- In total, low levels of citrate in the urine increase risk of stone formation.

Treatment

- Correction of acidosis or hypokalemia
- Potassium bicarbonate or potassium citrate (sodium alkali will increase Ca excretion
- Pak and Fuller showed benefit of Potassium citrate in increasing urinary citrate levels and in reduction of calcium oxalate supersaturation

Idiopathic Calcium Lithiasis
34 percent

- Normocalciuric and free of metabolic abnormalities
- Treatment difficult to fashion. Hydration, Ca restriction, and avoidance of foods high in oxalate have limited effectiveness.
- Ettinger, Coe, and Parks observed recurrence of stones in more than half of patients during 2 to 3 years of treatment with diet and hydration.
- Orthophosphate effectiveness is uncertain.

Low Calcium Diet

- Ettinger and Kolb found that a low Calcium diet reduced stone formation from 57 stones/100 patient years to 33 stones/100 patient years in a study of 46 patients (6 year study)
- Acid phosphate supplementation appeared to offset the beneficial effect of calcium restriction
- Patients served as there own controls and hard to say if diet restriction beneficial or if stone disease simply waned over time

Thiazide and Allopurinol

- 30 patients were treated with this combination of drugs to try to lower the calcium oxalate activity product and reduce the availability of heterogeneous nuclei
- Therapeutic response much less evident when compared to same treatment for hypercalciuric and hyperuricosuric patients on same drug.
- Yendt found that thiazide diuretic alone reduced rate of stone recurrence in idiopathic stone formers

Hyperoxaluria

- Most stone formers excrete no more oxalate than do normal people
- Excessive urinary oxalate excretion does occur in some people and causes stones by raising the saturation of the urine with respect to calcium oxalate
- When severe, nephrocalcinosis, TI nephritis, functional defects of the renal tubule, azotemia, and renal failure have been reported

Production of Oxalate

- Humans cannot metabolize oxalate, renal excretion is sole route of elimination
- freely filtered but conflicting results as to whether there is net secretion or reabsorption in the tubules
- Amount in urine is sum total of de novo synthesis and intestinal absorption

Production of Oxalate

- Oxidation of ascorbic acid (35%) and oxidation of glyoxylate.
- Lactate dehydrogenase probably responsible for most oxalate production

Classification of Hyperoxaluria

Metabolic overproduction

- Hereditary
- Pyridoxine def
- ethylene glycol ingestion
- Methoxyflurane anesthesia

GI Overabsorption

- oxalate overingestion
- ileal resection
- pancreatic insuff.
- Celiac sprue
- small bowel bypass
- Crohn’s disease
- cellulose phos ingestion

Oxalate

- Dietary intake varies from 400 to 900mg/day dep on consumption of green leafy vegetables
- 2-4.5 percent absorbed
- Calcium restriction, bile salts, and long chain fatty acids increase oxalate absorption
- Positive correlation between fecal fat and hyperoxaluria: increased luminal fatty acids may be critical in development of oxalate overabsorption. (enteric hyperoxaluria)

Acute Management

- Narcotic analgesics
- IV fluids
- Treatment of infection
- Possible hospitalization (sepsis, obstruction, intractable pain or vomiting)
- <4mm 93% pass, >8mm rarely pass